# Congenital erythrocytosis

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**Congenital Erythrocytosis**

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**Summary**

Congenital erythrocytosis is by definition present from birth. Patients frequently present in childhood or as young adults and a family history may be present. The erythrocytosis can be primary where there is an intrinsic defect in the erythroid compartment or secondary where increased erythropoietin production from some source leads to an erythrocytosis. Primary causes include erythropoietin receptor mutations. Congenital secondary causes include mutations in the genes involved in the oxygen sensing pathway and haemoglobins with abnormal oxygen affinity and very rare causes such as bisphosphoglycerate mutase deficiency and hereditary ATP increase. Having established that a congenital erythrocytosis is a likely diagnosis, molecular investigations should be carried out looking for described molecular abnormalities. A congenital erythrocytosis may be an incidental finding but non-specific symptoms are described. Major thromboembolic events have been noted in some cases. Pulmonary hypertension has also been reported in some cases. Low dose aspirin and venesection are therapeutic manoeuvres which should be considered in managing these patients. In those with Chuvash polycythaemia with VHL mutations JAK inhibition may prove to be a useful therapeutic option.

**Keywords:** Congenital erythrocytosis, erythropoietin, erythropoietin receptor, oxygen sensing pathway, high affinity haemoglobin.

**Introduction**

An erythrocytosis is present when the red cell mass is greater than 125% of predicted for sex and body mass. This usually correlates with an elevated Haemoglobin (HB) and/or Haematocrit (Hct) although not always As the work of Johansson and colleagues demonstrates it is possible to have a raised red cell mass with a normal Hb or Hct [1]. However, an Hct above 0.60 in a male and 0.56 in a female always reflects an increased red cell mass. A congenital erythrocytosis by definition is present from birth and is therefore thought to be due to a germline defect. It can be and is usually detected when a blood check is carried out in a young child or in early adult lifebut ,as awareness of these defects grows testing is more widespread and thus it may be much later before it is detected.

An erythrocytosis congenital or otherwise is classified as primary where there is an intrinsic defect in the bone marrow precursors driving the red cell production. In primary erythrocytosis the erythropoietin (EPO) level is reduced below normal commensurate with a primary erythroid defect. In contrast in a secondary erythrocytosis a factor extrinsic to the bone marrow is driving the red cell production. This is usually EPO from some source. Therefore in a secondary erythrocytosis the EPO levels are either elevated or normal (which is inappropriate for a raised HB and therefore reflects the increased EPO drive to erythropoiesis). With congenital erythrocytosis, germline defects have been identified in some cases which result in either a primary or secondary defect where the molecular lesion results in increased EPO production.

The known causes of a congenital erythrocytosis are listed in Table 1 and will be discussed.

**Primary Congenital Erythrocytosis**

**Erythropoietin Receptor**

A cytokine links with its receptor on the cell surface. Once this occurs then a number of downstream processes take place leading to cell signalling and cell production. EPO is one such cytokine which links on the cell surface to the erythropoietin receptor (EpoR). When this happens, the proteins JAK2 and STAT5 autophosphorylate, STAT5 dimerises, translocates to the nucleus, and then triggers downstream signalling and production of red cells. The process is then turned off when a further protein SHP-1 attaches to its docking site and down-modulates the receptor. However, mutations occur in the gene for the *EpoR* which lead to premature stop codons and a truncated receptor. The truncated receptor looses the SHP-1 docking site and thus once EPO attaches to the receptor it is switched on but does not get switched off again and therefore continues to drive red cell production without further EPO stimulation (Figure 1).The first such *EpoR* mutation was described in an Olympic medal winning cross country skier who was part of a large family where many members had erythrocytosis [2] At least 11 mutations in the *EpoR* have been described which lead to a truncated receptor and erythrocytosis [3] and therefore *EpoR* mutations are infrequently found as a cause of primary congenital erythrocytosis usually in young adults.

***LNK* mutations**

The lymphocyte adaptor protein (LNK) is involved in cell signalling and is a negative regulator of the cytokine signalling by attenuating JAK activation. This includes the EPO signalling pathway and it is shown that Lnk via the SH2 domain negatively regulates EpoR signalling by attenuating Jak2 activation and thus EPO mediated erythropoiesis [4] Mutations have been described in *LNK* in myeloproliferative neoplasms. These mutations result in a defective LNK protein which does not act as a negative regulator of the JAK/ STAT pathway downstream of the cytokine attachment to it's receptor and thus lead to increases downstream erythropoiesis and a primary erythrocytosis (with an associated low EPO level) [5]. In several cases the mutation was shown to be in the germline [6]. *LNK* mutations have also been described in a small number of reports of idiopathic erythrocytosis and it is postulated that this may be a possible explanation for idiopathic erythrocytosis in some instances [7]. In these cases the germline status has mainly not been investigated. However as germline mutations have been described in myeloproliferative neoplasms there is a least the possibility that a germline *LNK* mutations could be found accounting for congenital erythrocytosis.

**Secondary Congenital Erythrocytosis**

**The oxygen sensing pathway**

The human organism has a sensitive mechanism for sensing oxygen and responding to hypoxia. This involves a number of proteins. This system consists of the prolyl hydroxylases (PHDs) which have three isoforms PHD1, PHD2 and PHD3. In normoxia, the PHDs hydroxylate hypoxia-inducible factor (HIF) which consists of both an alpha and a beta subunit. When hydroxylation occurs, the von-Hippel-Lindau tumour suppressor protein (VHL) is bound. This is a substrate recognition unit of the E3 ubiquitin ligase complex. Ubiquitination and degradation of HIF then occurs in the proteasome and thus low HIF levels are maintained in normoxia. In contrast with hypoxia, less hydroxylation occurs, HIF escapes VHL mediated degradation. Levels of HIF alpha then rise and it dimerises with the beta subunit. The combined HIF protein translocates to the nucleus and binds to the hypoxia response element in the 3' region of the target genes. This then leads to HIF regulated transcription and production of a number of proteins including those involved in glycolysis, glucose uptake, angiogenesis and EPO (Figure 2) [8].

## Mutations of the oxygen sensing pathway

### *PHD2*

A first in man mutation in the *PHD*2 (*EGLN1*) gene was discovered in a family with erythrocytosis, a heterozygous change C950G leading to a protein alteration of proline to arginine at codon 317 [9].Two affected siblings all had mild erythrocytosis with normal or increased EPO levels while an unaffected had normal haematology and did not have the mutation. Of interest the other parent who was deceased had been treated for polycythaemia for some years and the mutation was detected in tissue from this individual. *In vitro* studies showed that the mutation had abnormal activity with decreased HIF binding and decreased HIF inhibitory activity supporting that the mutation would lead to erythrocytosis. A mouse model of the mutation provided further evidence that this mutation as a cause of erythrocytosis [10]. A number of further mutations in *PHD2* have now been documented in individuals with congenital erythrocytosis [11]. One of these has been identified in a nearby codon in PHD2, resulting in an A1121G change and a His374Arg amino acid substitution. This individual, thirteen years after presentation, was found to have a paraganglioma. The mutation was also found in the tumour tissue absence of the wild type *PHD2* allele thus loss of heterozygosity. This suggests in this case that *PHD2* was acting as a tumour suppressor gene. Of note, paragangliomas are vascular tumours and up-regulation of the HIF pathway may contribute to tumour growth.

Thus *PHD*2 mutations are clearly an explanation in some cases for a secondary congenital erythrocytosis. To date no mutations have been discovered in the other *PHD* genes

### *VHL*

The first defects in the oxygen sensing pathway were discovered in the VHL gene. A homozygous mutation in the *VHL* gene C598T was identified in a large cohort of individuals with erythrocytosis in the remote upper Volga region of Russia, Chuvashia [13]. In this remote area with a population of just over one million, erythrocytosis was known to be endemic. Over a hundred individuals from more than 80 families had Hbs usually over 200g/L, normal or elevated EPO levels and inheritance was autosomal recessive. Investigation lead to the VHL gene as the candidate gene and sequencing identified the homozygous mutation. The mutant protein was shown to have had reduced activity as a negative regulator of HIF-1 dependent gene transcription and result in increased expression of HIF-1 regulated genes target genes including *EPO* [13]. VHL protein is a tumour suppressor but there is no increase in malignancy found in those with Chuvash polycythaemia. This homozygous mutation in the *VHL* gene has been identified in other patients with congenital erythrocytosis from other areas of the world. A number of sporadic cases have been identified in the UK and Ireland but many of these were of Pakistani or Bangladeshi origin [14]. A large cohort, actually with a higher gene frequency that in Chuvashia, have been identified in the Italian island of Ischia [15]. Many of these groups have been looked at further and a common founder has been potentially identified [16]. A few compound heterozygotes of the *VHL* gene with erythrocytosis have also been seen [11]. There are also a few cases where there is only a heterozygote change with the other *VHL* allele normal and intact. It is not clear in these cases how erythrocytosis results but another undiscovered lesion has to be postulated [17].

### *HIF2A*

The first mutation in *HIF2A* (*EPAS*1) was a gain-of –function mutation which was identified in 3 generations of a family associated with erythrocytosis. The propositus presented at the age of 23 years. His mother and grandmother were also known to have erythrocytosis and they were found to carry the same mutation whereas unaffected family members did not have the mutation. These individuals had a G1609T change leading to a change at codon 537 from glycine to tryptophan. Gly 537 is an amino acid which is highly conserved across species in all HIF-2$\alpha$ proteins. It is also near to the residue Pro531 which is the primary hydroxylation site in HIF-2$\alpha$ and is not present in the other HIF-1$\alpha$ and HIF-3$\alpha$ proteins. Therefore this residue is likely to be of importance. *In vitro* studies showed that the altered protein binds PHD2 and VHL differently that wild type protein, is degraded more slowly, and induces downstream genes supporting a mutant protein which has a gain-of -function [18]. Other gain-of-function mutations in *HIF2A* associated with congenital erythrocytosis have been identified in other kindred. These result in amino acid changes in the same or nearby residues [19, 20].

Another family with 4 generations who had erythrocytosis, was found to have the Gly537Arg mutation. In this kindred 2 affected individuals had pulmonary hypertension in their sixth decade with no evidence of thromboembolism. Expression of mutants in a cell line showed that there was increased activity with the Gly537Arg mutant compared to wild type and that the Gly 537Arg mutant was more active than the original Gly 537Trp mutant which may be consistent with the severe phenotype in these kindred [21].

### *BPGM*

In the red cell, 2,3 bisphosphoglycerate (2,3-BPG) binds to the haemoglobin and converts the haemoglobin molecule to a low oxygen affinity state shifting the oxygen affinity curve to the right. Deficiency of 2,3-BPG moves the oxygen affinity curve to the left and the haemoglobin is kept in a high oxygen affinity state. With a state of high oxygen affinity of haemoglobin oxygen is not delivered to tissues and a compensatory erythrocytosis results. In the glycolytic pathway, the production of 2,3-BPG involves the conversion of 1,3 BPG to 2,3 BPG which is catalysed by bisphosphoglycerate mutase (BPGM). Mutations in the *BPGM* gene lead to an abnormal functioning BPGM and deficiency of 2,3-BPG, thus shifting the oxygen affinity curve to the left and congenital erythrocytosis [22]. Autosomal dominant and recessive cases have been described. These mutations are extremely rare and assays for BPMG and 2,3 BPG are now very difficult to get carried out. Recently a Caucasian who had presented with erythrocytosis at the age of 27 years and had been extensively investigated for other oxygen sensing pathway mutations had a novel missense mutation in the *BPGM* gene with a G268A substitution resulting in the substitution of arginine with histidine at residue 90 (R90H) was identified by whole-genome sequencing [23]. As this technology comes into widespread use it is likely that other such mutations may be discovered.

**High oxygen affinity haemoglobins**

Oxygen is transported to the tissues bound to haemoglobin in the blood. The oxygenation and deoxygenation of haemoglobin occurs at the heme iron binding site and the affinity for oxygen depends on the haemoglobin. This is expressed by the shape of the haemoglobin-oxygen dissociation curve. An high oxygen affinity haemoglobin, has a left shifted haemoglobin oxygen dissociation curve, oxygen is tightly bound, and not easily released to the tissues. At tissue level this results in a relative, hypoxia, EPO production and as a result secondary erythrocytosis.

The first reported high oxygen affinity haemoglobin was Haemoglobin Chesapeake and approximately 100 high oxygen affinity variants have been described both $\alpha$ and $\beta$ globin gene mutations resulting in stable and unstable haemoglobins. These have an autosomal dominant inheritance and therefore there is often a family history to be elicited. Individuals often present with erythrocytosis and investigation for a high affinity Hb should be considered24].A p50 calculation should be carried out. This can be done on routine blood gas analysers. Sequencing of the globin genes will identify and mutations and with the widespread use of molecular testing this may be the easiest way to look for these defects.

**Methaemoglobinaemia**

Normally 1% of haemoglobin is in the methaemaehoglobin form. Methemoglobin impairs oxygen binding and transport and if a large amount of haemoglobin is in the methemoglobin form then cyanosis results and a compensatory erythrocytosis develops. Congenital methemoglobinaemia can arise either because of a deficiency cytochrome $b_5$ reductase or an abnormal M Haemoglobin.

Abnormal M haemoglobins are inherited in an autosomal dominant manner and $\alpha$,$\beta$,and $\gamma$ globin variants have been reported[25]. In an $\alpha$ chain variant cyanosis will be present from birth while with a $\beta$ chain variant cyanosis will not appear until 3 months postpartum as the changeover from fetal to adult haemoglobin occurs. This observation may help in diagnosing the cause of the cyanosis. NADH-cytochrome $b_5$ reductase also leads to methaemoglobinaemia. NADH-cytochrome $b_5$reductase catalyzes electron transfer from NADH to cytochrome $b_5$ and is encoded by the *CYB5R3* gene. Over 40 mutations of this gene have been described and inheritance is autosomal recessive. Type 1 mutations lead to a defect in the erythrocytes only whereas type 11 mutations have accompanying neurological defects [26]

**Inherited increased ATP**

Erythrocytosis has been reported in families who have been described with increased ATP levels associated with low 2.3-BPG levels with autosomal dominant inheritance. Elevated pyruvate kinase activity has been associated but the relationship is not fully explained [27]. These extremely rare described defects should perhaps be considered as causes of congenital erythrocytosis.

**Investigation**

Investigation of a congenital erythrocytosis starts with careful history and examination. In the history features which could indicate a congenital cause include an early age of onset and a family history. It is necessary to explore for other causes of erythrocytosis in the history and on examination in order to eliminate other reasons. Laboratory investigation commences with a repeat blood count for confirmation. Next an EPO level will indicate, depending on the result, whether the erythrocytosis is primary or secondary. If it is not clear that there is a true erythrocytosis a red cell mass study should be carried out to confirm that the red cell mass is greater than 125% of predicted. A $P_{50}$ test can be carried out to examine oxygen affinity in the patient if available. Haemoglobin electrophoresis may also be useful to look for abnormal haemoglobins although if may be preferred to look directly at the globin genes for mutations. Molecular analysis can there be carried out with sequencing of individual genes where mutations have been described (Table 2). This requires a considerable amount of laboratory time effort. It is probable that in the future this will be done in more comprehensive next generation sequencing panels.

**Clinical consequences**

The clinical effects of congenital erythrocytosis are very variable. In many patients the erythrocytosis is an incidental finding. However, they may come to clinical attention because of vague symptoms which may be associated with hyperviscosity. Symptoms such as weakness, fatigue, headache, blurred vision and slow mentation may be described. On examination a plethoric appearance may be noted.

Complications are those associated with hyperviscosity and the main events described are thromboembolic events. In the Chuvash cohort with the homozygous *VHL* mutation retrospectively, life expectancy was reduced compared to controls and causes of death were thromboembolic [28]. All there cases are very rare and there is no clear pattern of events. However, there are reports of serious, life threatening and unusual thromboembolic events occurring in young individuals with oxygen sensing pathway mutations [17]. There are now also reports that pulmonary hypertension may occur in some of these cases and it is necessary to consider screening for this complication [21].

**Management**

Congenital erythrocytosis is very rare and there is little evidence to guide management. There are some options which should be considered. Low dose aspirin has been shown to be of use for prophylaxis of thromboembolic events in the acquired disorder polycythaemia and there is rationale to consider this in congenital erythrocytosis in those who do not have a contraindication to aspirin. It should be noted however, that in retrospective studies, there was no relationship between aspirin use and outcome in Chuvash polycythaemia [28].

Venesection will reduce the Hct and blood viscosity and potentially could reduce the risk of thromboembolic events. It is of note that the relationship between reduction of the Hct and thromboembolic events in the Chuvash cohort was not conclusive. In should also be noted that in some at least of the oxygen sensing mutations the effect of the mutation is an abnormal physiology and the raised Hct may be required for functioning with the defect [29]. The other physiological issue which must be considered is that in those the erythrocytosis results from a left shifted oxygen dissociation curve, oxygen delivery to the tissues is reduced and there is relative tissue hypoxia so the raised Hct may be required to deliver enough oxygen to the tissues.

It may also be very difficult to reduce the Hct by venesection by a meaningful amount particularly in those with very high Hcts. Nevertheless it may be reasonable to consider venesection to reduce the Hct particularly in those with symptoms (dizziness, dyspnoea and others). Response to venesection should then be assessed.

It has recently been shown in mice that the Chuvash VHL mutants have an altered affinity for the cytokine signalling-1 (SOCS1) and do not degrade JAK2 [30]. As JAK inhibitors are now available in clinical practice they have been tried with some shown efficacy in several Chuvash patients [31]. JAK inhibitors may prove to be a useful therapeutic option for those with the congenital erythrocytosis of the Chuvash variety in the future.

**Conclusion**

Rare individuals presenting often at a young age and perhaps with a family history may have a congenital erythrocytosis. They should be investigated for known primary or secondary causes of erythrocytosis by molecular investigations. Aspirin and venesection are the main therapeutic options that can be considered although there is little evidence to support therapeutic decisions. However, in the majority of individuals currently no lesion can be identified.

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**Table 1: Causes of congenital erythrocytosis**

## Primary erythrocytosis

*EPO receptor* mutations

## Secondary erythrocytosis

Oxygen sensing pathway defects (*PHD2, VHL, HIF2A*)

Bisphosphoglycerate mutase deficiency

High oxygen affinity haemoglobin

Methaemoglobinaemia

Hereditary ATP increase

**Table 2 Investigations**

History and examination

Repeat confirmatory FBP

Red cell mass

Erythropoietin Level

$P_{50}$-Oxygen dissociation Curve

Haemoglobin Electrophoresis

Sequencing for known gene variations

**Legends for figures**

Figure 1 Erythropoeitin receptor

Erythropoietin docks with its receptor and autophosphorylates, JAK dimerises STAT and then signals to produce red cells. The receptor is down-modulated by SHP-1. A mutation in the gene leads to a truncated receptor which has lost the site of attachment of SHP-1 and therefore cannot be down-modulated and continues to signal to produce red cells without more erythropoietin.

Figure 2 Oxygen sensing pathway

In normoxia prolyl hydroxylases (PHDs) hydroxylate hypoxia inducible factor (HIF) which binds to von-Hippel-Lindau tumour suppressor protein (VHL). Ubiquitination and degradation of HIF then occurs in the proteasome. In hypoxic conditions HIF-2a in not degraded but binds to the Beta subunit, translocates to the nucleus and causes production of further proteins including erythropoietin.